**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| APPLICANTS: | Sanchez-Madrid, *et al.* | | |
| SERIAL NUMBER: | 10/770,639 | EXAMINER: | Zachary S. Skelding |
| FILING DATE: | February 2, 2004 | ART UNIT: | 1644 |
| FOR: | Immune Regulation Based On The Targeting Of Early Activation Molecules | | |

**Via EFS**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313.1450

**PRE-APPEAL BRIEF CONFERENCE REQUEST FOR REVIEW**

In reply to the Office Action mailed July 17, 2009, Applicant requests a Pre-Appeal Brief Conference for Review and submit the following Remarks. This paper is timely filed with a petition for one-month extension and appropriate fee if submitted on or before November 17, 2009. Applicant believes no additional fees are due. However, the Commissioner is hereby authorized to charge any fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-0311, Reference No. 27331-501 CIP2A.

**Remarks** begin on page 2 of this paper.

## REMARKS

The Office Action maintains two rejections under 35 U.S.C. § 103(a) that reject claims 56, 59, 60, and 105-108 citing Van der Lubbe[1/] as the primary reference in view of Marzio,[2/] McInnes 1997,[3/] McInnes 1998,[4/] and White.[5/] The Office Action, however, fails to provide a reasonable rationale for why the claimed invention would have been obvious.[6/]

The combination of reference fails to teach or suggest all elements of the claims. Van der Lubbe at least fails to disclose an anti-CD69 antibody that is capable of depleting $CD69^+$ T-cells. None of the secondary references disclose a depleting anti-CD69 antibody. Indeed, the examiner has acknowledged that neither McInnes 1998 nor McInnes 1997 teach the use of a depleting anti-CD69 antibody to treat rheumatoid arthritis (RA).[7/] The references alone or in combination thus fail to teach or suggest every element of the claims. The examiner fails to provide a reasonable rationale for why the missing elements would have been obvious.

Primarily, the combination of references fail to enable the *in vivo* use of any depleting anti-CD69 antibody molecule for the treatment of rheumatoid arthritis. Indeed, the references fail to enable any use of any depleting anti-CD69 antibody molecule. As such, this rejection necessarily fails because, as held by the Federal Circuit, **"[i]n order to render a claimed apparatus or method obvious, the prior art must enable one skilled in the art to make and use the apparatus or method."**[8/]

Further, the rationale used to support the present rejection also fails to provide how a person of ordinary skill in the art would have arrived at the present invention predictably and with a reasonable expectation of success. For example, Van der Lubbe teaches that memory T-cells resist the effect of CD4 antibodies. The examiner asserts that because of this teaching, one

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1/ *J Autoimmun.* 1997 Feb; 10(1):87-97.

2/ *Immunopharmacol Immunotoxicol.* 1999 Aug; 21 (3):565-82.

3/ *Nat Med.* 1997 Feb;3(2):189-95.

4/ *Immunol Today.* 1998 Feb; 19(2):75-9.

5/ U.S. Patent Publication No. 2002/0039557 A1.

6/ See MPEP § § 2143 and 2143.03.

7/ Final Office Action mailed 8/15/2007, page 5, fifth ($5^{th}$) full paragraph.

8/ See Motorola, Inc. v. Interdigital Tech. Corp., 121 F.3d 1461, 1471, 43 USPQ2d 1481, 1489 (Fed. Cir. 1997) ((*quoting* Beckman Instruments, Inc. v. LKB Produkter AB, 892 F.2d 1547, 1551, 13 USPQ2d 1301, 1304 (Fed. Cir. 1989))) (emphasis added).

of ordinary skill in the art would have immediately turned to CD69 to develop antibodies based on the teachings of Marzio and McInnes 1997. Marzio teaches that CD69 is expressed on memory T-cells and McInnes 1997 teaches that *non-depleting*, *neutralizing* CD69 antibody blocks TNF-α production in response to IL-15 *in vitro*. First, this same rationale was applied unsuccessfully in the prior art to CD4. Van der Lubbe teaches that despite the fact that CD4 is expressed on memory T-cells and that CD4 mAb was shown to block $CD4^+$ T-cell dependent immune response *in vitro*,[9/] further *in vivo* clinical studies with CD4 mAb should not aim at T-cell depletion due to the observance that memory T-cells resist the effect of CD4 antibodies.[10/] **There is nothing in Van der Lubbe or any cited secondary reference to suggest that a CD4 antibody could predictably be replaced with a CD69 antibody and that memory T-cells would not have also resisted the effect of CD69 antibodies.** Indeed, the data provided in the specification predicts that the *non-depleting*, *neutralizing* CD69 antibody used in McInnes 1997 would actually *exacerbate* an inflammatory condition such as RA.

In this regard, the cited references, alone or in combination, fail to teach or suggest with any specificity the use of a depleting CD69 antibody for the treatment of RA. Rather, the cited references highlight the complexity of the biology and discuss numerous molecules that are associated with an immune response. For example, should mere high expression of a molecule on memory T-cells be the deciding factor, then Van der Lubbe teaches that CD27 has a "persistent high expression" on the $CD45RO^+$ memory T-cells.[11/]

Rather, with the benefit of hindsight, the examiner has pieced together isolated teachings in several references to assert an obviousness rejection. In doing so, however, the examiner never analyzes or considers the references as a whole. Instead, the examiner exaggerates and overemphasizes isolated teachings of the cited references. When these references are read in their entirety, a different conclusion is reached. For example, the examiner emphasizes at page 7, first paragraph, of the Office Action that McInnes 1998 teaches that "T-cell-directed therapies that not only inhibits T-cell activation but also depletes T cells from the synovial compartment, or at least interfere with their membrane interactions, will probably be the most efficacious." When this sentence is read in context of the entirety of McInnes 1998, however, it becomes clear that McInnes 1998 is referring to IL-15 and/or CD4 as the targets for therapy, thereby teaching away

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9/ See Van der Lubbe at page 87, left column, first paragraph.

10/ See Van der Lubbe at page 95, right column, last paragraph.

11/ See Van der Lubbe at page 95, left column, lines 6-8.

from CD69. For example, the passage of McInnes 1998 cited by the examiner is contained in a paragraph that provides, in part, as follows (emphasis added):

> [D]iverse cell types within synovial membrane may exhibit coordinate proinflammatory activities through cell contact. … T-cell-directed therapies that not only *inhibit* T-cell activation but also *deplete* T cells from the synovial compartment, or at least *interfere* with their membrane interactions, will probably be the most efficacious. It is of interest that clinical improvement following CD4 therapy in RA correlates with synovial T-cell coating with anti-CD4.

When read as a whole, McInnes 1998 teaches IL-15 or IL-15 receptors may be targeted to *inhibit* T-cell activation and *interfere* with their membrane interactions. Specifically, McInnes 1998 teaches that "IL-15 can recruit T cells and … modify cell-cell interactions within inflammatory sites,"[12] that IL-15 expression is associated with rheumatoid arthritis,[13] and that "IL-15 can recruit and expand CD45R0+ memory cell subsets in the synovial membrane, in which, … newly recruited T-cells can produce TNF-α directly or via contact with macrophages."[14] Further, McInnes 1998 concludes with the following:

> The identification of IL-15-mediated T-cell and monocyte activation in the synovial membrane, … provides a novel target for such biological approaches. This might be either through direct neutralization of IL-15 or by targeting IL-15 receptors.

With regard to depletion therapies, in the paragraph cited by the examiner, McInnes 1998 references anti-CD4 therapy and cites the reference of Choy[15] that shows that the percentage of anti-CD4 monoclonal antibody-coated lymphocytes in the rheumatoid joint is associated with clinical improvement. Depletion therapy using a anti-CD69 antibody is never contemplated, which is not surprising as McInnes 1997 and McInnes 1998 are concerned with elucidating the role IL-15 in rheumatoid arthritis, not developing CD69 as a target. In this manner, the examiner exaggerates and overemphasizes the teachings of the prior art references by not considering the references as a whole, which is improper. It is well established that reliance on isolated teachings in the prior art that fails to consider the reference as a whole is improper. The Federal Circuit in Bausch & Lomb v. Barnes-Hind/Hydrocurve, Inc.[16] clearly instructs that cited references must be considered for all they teach, and not relied on to make "strawman"

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12/ McInnes 1998 at page 76, left column, lines 32-34.

13/ McInnes 1998 at Title. See also the entire document.

14/ McInnes 1998 at page 77, left column, lines 17-20.

15/ Choy et al., *Arthritis Rheum.* 39, 52-56 (1996).

16/ 796 F.2d 443, 447-49 (Fed. Cir. 1986), cert. denied, 484 U.S. 823 (1987)

arguments that highlight an isolated teaching of the reference. This point is restated in MPEP § 2141.02 (VI) as follows: "A prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention." The examiner fails to consider the cited references in their entirety.

Finally, even assuming, *arguendo*, that a person of ordinary skill in the art would have been motivated to use the *non-depleting, neutralizing* CD69 antibody used in McInnes 1997 for the treatment of RA,[17] the person of ordinary skill in the art would have been unsuccessful and would not have arrived at the present invention. The specification teaches, unexpectedly from the standpoint of one of ordinary skill in the art at the time the invention was made, that it is important that the CD69 specific antibody be a depletor of CD69+ cells, as opposed to specifically binding to CD69, while not depleting CD69+ cells in an *in vivo* model for unwanted immune response. Treatment of mice having collagen-induced arthritis (CIA) with a *non-depleting* CD69 specific antibody that does not deplete CD69+ cells *in vivo* (*i.e.*, mAb 2.2) actually *exacerbated* CIA in those mice.[18]

In view of the above, Applicants respectfully submit that (1) the rejection is based on a hindsight rationale that does not properly weigh evidence of unexpected results; (2) the examiner fails to consider the cited references as a whole, for all they teach; (3) the cited references, alone or in combination, do not enable the subject matter of the present claims; and (4) the cited references do not teach the use of a depleting CD69 antibody molecule with any specificity.

An indication of allowance of all claims is solicited. In the alternative, Applicants request reconsideration of the present rejection and a new Office Action that addresses the issues highlighted herein.

Respectfully submitted,

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17/ Applicants do not concede this point.

18/ *See e.g.*, Specification at page 105, lines 3-6.